

**PATENT COOPERATION TREATY**  
**PCT**  
**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**  
(Chapter II of the Patent Cooperation Treaty)  
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>x-16094</b>	<b>FOR FURTHER ACTION</b>		See Form PCT/IPEA/416
International application No. <b>PCT/US2004/039775</b>	International filing date ( <i>day/month/year</i> ) <b>21.12.2004</b>	Priority date ( <i>day/month/year</i> ) <b>22.12.2003</b>	
International Patent Classification (IPC) or national classification and IPC <b>A61K31/4196, A61K31/4245, A61K31/433, C07D249/08, C07D271/10, C07D285/12, A61P3/10</b>			
<p><b>Applicant</b> <b>ELI LILLY AND COMPANY</b></p>			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> (<i>sent to the applicant and to the International Bureau</i>) a total of 9 sheets, as follows:</p> <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</li> <li><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</li> </ul> <p>b. <input type="checkbox"/> (<i>sent to the International Bureau only</i>) a total of (indicate type and number of electronic carrier(s)), containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Box No. I Basis of the opinion</li> <li><input type="checkbox"/> Box No. II Priority</li> <li><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li><input type="checkbox"/> Box No. IV Lack of unity of invention</li> <li><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li><input type="checkbox"/> Box No. VI Certain documents cited</li> <li><input type="checkbox"/> Box No. VII Certain defects in the international application</li> <li><input type="checkbox"/> Box No. VIII Certain observations on the international application</li> </ul>			
Date of submission of the demand <b>11.10.2005</b>	Date of completion of this report <b>13.01.2006</b>		
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer <b>Cortés, J</b> Telephone No. +49 89 2399-8206		

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IAP20 Rec'd PCT/PTO 19 MAY 2006

**Box No. I Basis of the report**

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
  - This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
    - international search (under Rules 12.3 and 23.1(b))
    - publication of the international application (under Rule 12.4)
    - international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the elements\* of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

**Description, Pages**

1-135 as originally filed

**Claims, Numbers**

1-83, 84(part 1) as originally filed  
84(part 2), 85-87 filed with telefax on 11.10.2005

- a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3.  The amendments have resulted in the cancellation of:
    - the description, pages
    - the claims, Nos.
    - the drawings, sheets/figs
    - the sequence listing (*specify*):
    - any table(s) related to sequence listing (*specify*):
  4.  This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
    - the description, pages
    - the claims, Nos.
    - the drawings, sheets/figs
    - the sequence listing (*specify*):
    - any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application,  
 claims Nos. 57-61,63,65,65

because:

- the said international application, or the said claims Nos. 57-61,63,65,65 relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):  
 the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.  
 no international search report has been established for the said claims Nos.  
 the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

- has not been furnished  
 does not comply with the standard

the computer readable form

- has not been furnished  
 does not comply with the standard

- the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

- See separate sheet for further details

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes: Claims	
	No: Claims	1-87
Inventive step (IS)	Yes: Claims	
	No: Claims	1-87
Industrial applicability (IA)	Yes: Claims	1-56, 62, 64, 67-87
	No: Claims	

**2. Citations and explanations (Rule 70.7):**

**see separate sheet**

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**Re Item I**

**Basis of the opinion**

With fax of 11.10.2005 the Applicant has filed three new dependent claims 85 to 87 without indicating the basis for these new claims in the application as originally filed.

These claims seem to be based on claim 1 as originally filed by deleting meanings in the definition of substituents (e.g. in new claim 85 the following meanings have been deleted: W=O,S; Y=single bond; E=A) and by replacement of unclear meanings by more specific meanings disclosed in the general part of the description (e.g. claim 85: "aliphatic linker" has been replaced by "C1-C6 alkyl" in the definition of U; the basis for this amendment can be found on page 14, lines 5 and 11 of the application as originally filed).

The new claims seem to have basis in the application as originally filed (e.g. the combination of features W=N and E=C(R3)(R4)A which has been singled out in new claim 85 has a basis e.g. in claim 8 as originally filed; new claims 86 and 87 are directed to compounds wherein W=S and W=O, respectively), i.e. comply with the requirements of article 34(b) PCT.

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The present claim set encompassed so many compounds that it is impossible to cite all documents which are relevant to the issue of novelty. The 9 X-documents cited in the search report have been cited only exemplarily.

The search has therefore been limited to compounds of the present claim 1 wherein V is a C0-8-alkyl, Y is C, O, S or N (i.e. not a single bond) and E is C(R3R4)A.

It is noted that new claims 85-87 also extend beyond the searched scope, since the definition of the linker V has not been limited.

Claims 57-61, 63, 65 and 66 relate to subject matter considered by this Authority to be

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covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

The following documents have been cited in the International Search Report:

- D1: WO 03/084916 A (WARNER-LAMBERT) 16 October 2003 (2003-10-16)
- D2: MEANWELL ET AL: JOURNAL OF MEDICINAL CHEMISTRY, vol. 35, no. 19, 1992, pages 3498-3512, XP002322862
- D3: EP-A-0 453 846 (BAYER) 30 October 1991 (1991-10-30)
- D4: US-A-3 637 672 (OSAKA SEIKA KOGYO) 25 January 1972 (1972-01-25)
- D5: WO 97/03967 A (RHONE-POULENC RORER) 6 February 1997 (1997-02-06)
- D6: JP 05 202038 A (SUMITOMO) 10 August 1993 (1993-08-10)
- D7: DATABASE BEILSTEIN 28 November 1988 (1988-11-28), XP002322768 Database accession no. BRN: 677345
- D8: DATABASE BEILSTEIN 1988, XP002322769 Database accession no. BRN: 1008075
- D9: DATABASE BEILSTEIN 1988, XP002322863 Database accession no. BRN: 1013052
- D10: WO 02/46174 A (GLAXO) 13 June 2002 (2002-06-13)

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**Novelty (Article 33(2) PCT)**

D1 to D9 disclose compounds which are encompassed by the present claim set. The present claim set is therefore not novel.

In the above mentioned fax the Applicant alleges that the three new claims 85-87 comply with the requirements for novelty, without explaining which specific structural feature or combination of features defines the difference to the prior art.

In new claims 85-87 the Applicant has merely excluded matter which had not been searched anyway (i.e. deletion of Y=single bond and E=A). I.e. the matter of new claims 85-87 can hardly have been delimited from the cited prior art. The generic groups defined in claims still overlap with the generic groups disclosed in the prior art and the specific prior art compounds cited in the search report are still encompassed by claims 85-87.

**Inventive Step (Article 33(3) PCT)**

D1 and D10 disclose PPAR modulators, D1 can be regarded as the closest prior art.

The problem of the application was the provision of new PPAR modulators.

Since the present compounds have already been disclosed in D1 the present invention lacks an inventive step.

In the above mentioned fax the Applicant alleges that the three new claims 85-87 comply with the requirements for inventive step, without explaining which specific structural feature or combination of features defines the contribution to the prior art, why the chose of this feature was not obvious in view of D1 and/or D2 and whether this particular structural feature causes an unexpected improvement (e.g. higher pharmacologic activity).

**Clarity (Article 6 PCT)**

The claims contain many definitions and expression which are unclear within the meaning of Article 6 PCT, e.g. the terms "heteroalkyl", "heterocycloalkyl", the definition for an

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"aliphatic linker" (which could be according to the definition in claim 1 e.g. an oxygen atom) and the definition of R32 as a bond.

In the above mentioned fax the Applicant alleges that the claims are clear, since the general part of the description discloses clear definitions for the above mentioned terms.

This is not sufficient. Article 6 PCT requires the claims to be clear *per se*, i.e. without the need of referring to the description and it also does not resolve the problem of definitions which are inconsistent with the common meaning in the art.

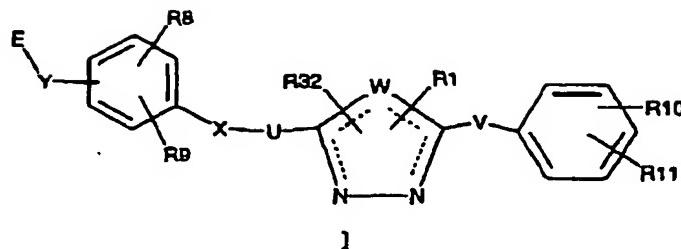
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- from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C<sub>1</sub>-C<sub>6</sub> alkyl;
- (j) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylene, C<sub>1</sub>-C<sub>6</sub> alkyl-COOR12'', C<sub>0</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyloxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, aryl-C<sub>0</sub>.4-alkyl, aryl- C<sub>1</sub>.4-heteroalkyl, heteroaryl-C<sub>0</sub>.4-alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0</sub>.2-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', OS(O)<sub>2</sub>R16', N(R17')<sub>2</sub>, NR18'C(O)R19', NR20'SO<sub>2</sub>R21', SR22', S(O)R23', S(O)<sub>2</sub>R24', and S(O)<sub>2</sub>N(R25')<sub>2</sub>; and wherein aryl-C<sub>0</sub>.4-alkyl, aryl- C<sub>1</sub>.4-heteroalkyl, heteroaryl-C<sub>0</sub>.4-alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0</sub>.2-alkyl are each optionally substituted with from one to three independently selected from R28; and wherein R10 and R11 optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound;
- (k) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;
- (l) R30 is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, aryl-C<sub>0</sub>.4-alkyl, aryl- C<sub>1</sub>.4-heteroalkyl, heteroaryl-C<sub>0</sub>.4-alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0</sub>.2-alkyl, and wherein C<sub>1</sub>-C<sub>6</sub> alkyl, aryl-C<sub>0</sub>.4-alkyl, aryl- C<sub>1</sub>.4-heteroalkyl, heteroaryl-C<sub>0</sub>.4-alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0</sub>.2-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;
- (m) R32 is selected from the group consisting of a bond, hydrogen, halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, and C<sub>1</sub>-C<sub>6</sub> alkylloxy; and
- (n) —— is optionally a bond to form a double bond at the indicated position.
85. A compound as claimed by any one of Claims 1, 2, 3, and 8 through 55:

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and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

- 5       (a) R1 is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> alkenyl, hetero(C<sub>1</sub>-C<sub>8</sub>)alkyl, aryl-C<sub>0-4</sub>-alkyl, arylhetero(C<sub>1-4</sub>)alkyl, heteroaryl-C<sub>0-4</sub>-alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0-2</sub>-alkyl, and, wherein C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> alkenyl, aryl-C<sub>0-4</sub>-alkyl, arylhetero(C<sub>1-4</sub>)alkyl, heteroaryl-C<sub>0-4</sub>-alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0-2</sub>-alkyl are each optionally substituted with from one to three substituents independently selected from R1';
- 10      (b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-COOR12, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyloxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, aryloxy, aryl-C<sub>0-4</sub>-alkyl, heteroaryl, heterocyclo C<sub>5</sub>-C<sub>14</sub> alkyl, C(O)R13, COOR14, OC(O)R15, OS(O)<sub>2</sub>R16, N(R17)<sub>2</sub>, NR18C(O)R19, NR20SO<sub>2</sub>R21, SR22, S(O)R23, S(O)<sub>2</sub>R24, and S(O)<sub>2</sub>N(R25)<sub>2</sub>; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;
- 15      (c) V is selected from the group consisting of C<sub>0</sub>-C<sub>8</sub> alkyl and hetero(C<sub>1-6</sub>)alkyl;
- 20      (d) X is selected from the group consisting of a single bond, O, S, S(O)<sub>2</sub> and N;
- 25      (e) U is C<sub>1</sub>-C<sub>6</sub> alkyl wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30;
- (f) W is N;
- (g) Y is selected from the group consisting of C, O, S, and NH;
- (h) E is C(R3)(R4)A and wherein

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- (i) A is selected from the group consisting of carboxyl, tetrazole, C<sub>1</sub>-C<sub>6</sub> alkynitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R<sup>7</sup>:
- 5 (ii) each R<sup>7</sup> is independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, aryl C<sub>0</sub>-C<sub>4</sub> alkyl and C<sub>1</sub>-C<sub>6</sub> alkyl;
- (iii) R3 is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>5</sub> alkyl, and C<sub>1</sub>-C<sub>5</sub> alkoxy; and
- 10 (iv) R4 is selected from the group consisting of H, C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub> alkoxy, aryloxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and aryl C<sub>0</sub>-C<sub>4</sub> alkyl, and R3 and R4 are optionally combined to form a C<sub>3</sub>-C<sub>4</sub> cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R26;
- 15 (i) R8 is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkylene, and halo;
- (j) R9 is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkylene, halo, aryl-C<sub>0</sub>-C<sub>4</sub> alkyl, heteroaryl, C<sub>1</sub>-C<sub>6</sub> allyl, and OR29, and wherein aryl-C<sub>0</sub>-C<sub>4</sub> alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl;
- 20 (k) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylene, C<sub>1</sub>-C<sub>6</sub> alkyl-COOR12'', C<sub>0</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyloxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, aryl-C<sub>0</sub>-C<sub>4</sub>-alkyl, arylhetero(C<sub>1</sub>-C<sub>4</sub>)alkyl, heteroaryl-C<sub>0</sub>-C<sub>4</sub>-alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0</sub>-C<sub>2</sub>-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', OS(O)<sub>2</sub>R16', N(R17')<sub>2</sub>, NR18'C(O)R19', NR20'SO<sub>2</sub>R21', SR22', S(O)R23', S(O)<sub>2</sub>R24', and S(O)<sub>2</sub>N(R25')<sub>2</sub>; and wherein aryl-C<sub>0</sub>-C<sub>4</sub>-alkyl, arylhetero(C<sub>1</sub>-C<sub>4</sub>)alkyl, heteroaryl-C<sub>0</sub>-C<sub>4</sub>-alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0</sub>-C<sub>2</sub>-alkyl are each
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optionally substituted with from one to three independently selected from R28; and wherein R10 and R11 optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound;

(l) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23',

5 R24', and R25' are each independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

(m) R30 is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, aryl-C<sub>0-4</sub>-alkyl,

arylhetero(C<sub>1-4</sub>)alkyl, heteroaryl-C<sub>0-4</sub>-alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0-2</sub>-

alkyl, and wherein C<sub>1</sub>-C<sub>6</sub> alkyl, aryl-C<sub>0-4</sub>-alkyl, arylhetero(C<sub>1-4</sub>)alkyl, heteroaryl-

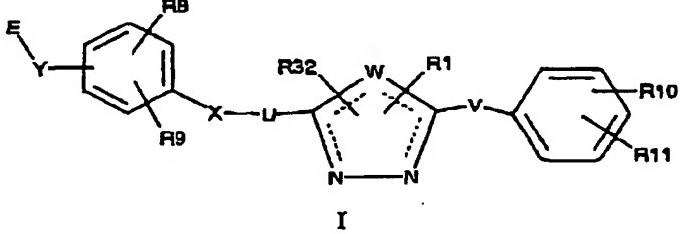
10 C<sub>0-4</sub>-alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0-2</sub>-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;

(n) R32 is selected from the group consisting of a bond, hydrogen, halo, C<sub>1</sub>-C<sub>6</sub> alkyl,

C<sub>1</sub>-C<sub>6</sub> haloalkyl, and C<sub>1</sub>-C<sub>6</sub> alkyloxo; and

(o) — is optionally a bond to form a double bond at the indicated position.

15 86. A compound as claimed by any one of Claims 1, 4, 5, 7, and 11 through 43:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

20 (a) R1 is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub>

alkenyl, hetero(C<sub>1</sub>-C<sub>8</sub>)alkyl, aryl-C<sub>0-4</sub>-alkyl, arylhetero(C<sub>1-4</sub>)alkyl, heteroaryl-

C<sub>0-4</sub>-alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0-2</sub>-alkyl, and, wherein C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-

C<sub>8</sub> alkenyl, aryl-C<sub>0-4</sub>-alkyl, arylhetero(C<sub>1-4</sub>)alkyl, heteroaryl-C<sub>0-4</sub>-alkyl, C<sub>3</sub>-C<sub>6</sub>

cycloalkylaryl-C<sub>0-2</sub>-alkyl are each optionally substituted with from one to three

25 substituents independently selected from R1';

(b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-

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COOR12, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyloxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl,  
aryloxy, aryl-C<sub>0-4</sub>-alkyl, heteroaryl, heterocyclo C<sub>5</sub>-C<sub>14</sub> alkyl, C(O)R13,

COOR14, OC(O)R15, OS(O)<sub>2</sub>R16, N(R17)<sub>2</sub>, NR18C(O)R19, NR20SO<sub>2</sub>R21,  
SR22, S(O)R23, S(O)<sub>2</sub>R24, and S(O)<sub>2</sub>N(R25)<sub>2</sub>; R12, R13, R14, R15, R16, R17,  
R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected  
from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;

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(c) V is selected from the group consisting of C<sub>0</sub>-C<sub>8</sub> alkyl and hetero(C<sub>1-6</sub>)alkyl;

(d) X is selected from the group consisting of a single bond, O, S, and N;

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(e) U is C<sub>1</sub>-C<sub>6</sub> alkyl wherein one carbon atom of the aliphatic linker is optionally  
replaced with O, NH or S, and wherein such aliphatic linker is optionally  
substituted with from one to four substituents each independently selected from  
R30;

(f) W is S;

(g) Y is selected from the group consisting of C, O, S, and NH;

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(h) E is C(R3)(R4)A and wherein

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(i) A is selected from the group consisting of carboxyl, tetrazole, C<sub>1</sub>-C<sub>6</sub>  
alkynitrile, carboxamide, sulfonamide and acylsulfonamide; wherein  
sulfonamide, acylsulfonamide and tetrazole are each optionally  
substituted with from one to two groups independently selected from  
R<sup>7</sup>;

(ii) each R<sup>7</sup> is independently selected from the group consisting of  
hydrogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, aryl C<sub>0</sub>-C<sub>4</sub> alkyl and C<sub>1</sub>-C<sub>6</sub> alkyl;

(iii) R3 is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>5</sub> alkyl,  
and C<sub>1</sub>-C<sub>5</sub> alkoxy; and

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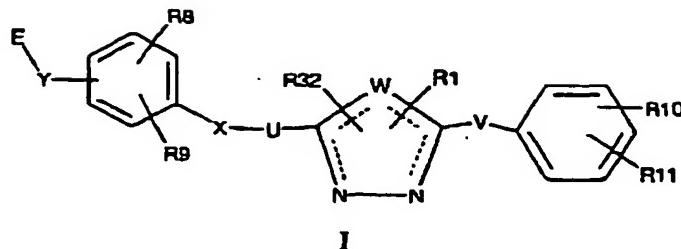
(iv) R4 is selected from the group consisting of H, C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub>  
alkoxy, aryloxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and aryl C<sub>0</sub>-C<sub>4</sub> alkyl, and R3 and  
R4 are optionally combined to form a C<sub>3</sub>-C<sub>4</sub> cycloalkyl, and wherein  
alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally  
substituted with from one to three substituents each independently  
selected from R26;

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- (i) R8 is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkylene, and halo;
  - (j) R9 is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkylene, halo, aryl-C<sub>0</sub>-C<sub>4</sub> alkyl, heteroaryl, C<sub>1</sub>-C<sub>6</sub> allyl, and OR29, and wherein aryl-C<sub>0</sub>-C<sub>4</sub> alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl;
  - (k) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylene, C<sub>1</sub>-C<sub>6</sub> alkyl-COOR12'', C<sub>0</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyloxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, aryl-C<sub>0</sub>-4-alkyl, arylhetero(C<sub>1</sub>-4)alkyl, heteroaryl-C<sub>0</sub>-4-alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0</sub>-2-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', OS(O)<sub>2</sub>R16', N(R17')<sub>2</sub>, NR18'C(O)R19', NR20'SO<sub>2</sub>R21', SR22', S(O)R23', S(O)<sub>2</sub>R24', and S(O)<sub>2</sub>N(R25')<sub>2</sub>; and wherein aryl-C<sub>0</sub>-4-alkyl, arylhetero(C<sub>1</sub>-4)alkyl, heteroaryl-C<sub>0</sub>-4-alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0</sub>-2-alkyl are each optionally substituted with from one to three independently selected from R28; and wherein R10 and R11 optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound;
  - (l) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;
  - (m) R30 is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, aryl-C<sub>0</sub>-4-alkyl, arylhetero(C<sub>1</sub>-4)alkyl, heteroaryl-C<sub>0</sub>-4-alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0</sub>-2-alkyl, and wherein C<sub>1</sub>-C<sub>6</sub> alkyl, aryl-C<sub>0</sub>-4-alkyl, arylhetero(C<sub>1</sub>-4)alkyl, heteroaryl-C<sub>0</sub>-4-alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0</sub>-2-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;
  - (n) R32 is selected from the group consisting of a bond, hydrogen, halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, and C<sub>1</sub>-C<sub>6</sub> alkyloxo; and
  - (o) ---- is optionally a bond to form a double bond at the indicated position.
- 30 87. A compound as claimed by any one of Claims 1, 4, 6, 7, and 11 through 43:

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and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

- 5       (a) R1 is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> alkenyl, hetero(C<sub>1</sub>-C<sub>8</sub>)alkyl, aryl-C<sub>0-4</sub>-alkyl, arylhetero(C<sub>1-4</sub>)alkyl, heteroaryl-C<sub>0-4</sub>-alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0-2</sub>-alkyl, and, wherein C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> alkenyl, aryl-C<sub>0-4</sub>-alkyl, arylhetero(C<sub>1-4</sub>)alkyl, heteroaryl-C<sub>0-4</sub>-alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0-2</sub>-alkyl are each optionally substituted with from one to three substituents independently selected from R1';
- 10      (b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-COOR12, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyloxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, aryloxy, aryl-C<sub>0-4</sub>-alkyl, heteroaryl, heterocyclo C<sub>5</sub>-C<sub>14</sub> alkyl, C(O)R13, COOR14, OC(O)R15, OS(O)<sub>2</sub>R16, N(R17)<sub>2</sub>, NR18C(O)R19, NR20SO<sub>2</sub>R21, SR22, S(O)R23, S(O)<sub>2</sub>R24, and S(O)<sub>2</sub>N(R25)<sub>2</sub>; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;
- 15      (c) V is selected from the group consisting of C<sub>0</sub>-C<sub>8</sub> alkyl and hetero(C<sub>1-6</sub>)alkyl;
- 20      (d) X is selected from the group consisting of a single bond, O, S, and N;
- 25      (e) U is C<sub>1</sub>-C<sub>6</sub> alkyl wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30;
- (f) W is O;
- (g) Y is selected from the group consisting of C, O, S, and NH;
- (h) E is C(R3)(R4)A and wherein

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- (i) A is selected from the group consisting of carboxyl, tetrazole, C<sub>1</sub>-C<sub>6</sub> alkynitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R<sup>7</sup>;
- 5 (ii) each R<sup>7</sup> is independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> haloalkyl, aryl C<sub>0</sub>-C<sub>4</sub> alkyl and C<sub>1</sub>-C<sub>6</sub> alkyl;
- (iii) R3 is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>5</sub> alkyl, and C<sub>1</sub>-C<sub>5</sub> alkoxy; and
- 10 (iv) R4 is selected from the group consisting of H, C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub> alkoxy, aryloxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and aryl C<sub>0</sub>-C<sub>4</sub> alkyl, and R3 and R4 are optionally combined to form a C<sub>3</sub>-C<sub>4</sub> cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R26;
- 15 (i) R8 is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkylene, and halo;
- (j) R9 is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylene, halo, aryl-C<sub>0</sub>-C<sub>4</sub> alkyl, heteroaryl, C<sub>1</sub>-C<sub>6</sub> allyl, and OR29, and wherein aryl-C<sub>0</sub>-C<sub>4</sub> alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl;
- 20 (k) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylene, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyloxy, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, aryl-C<sub>0</sub>-C<sub>4</sub>-alkyl, arylhetero(C<sub>1</sub>-C<sub>4</sub>)alkyl, heteroaryl-C<sub>0</sub>-C<sub>4</sub>-alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0</sub>-C<sub>2</sub>-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', OS(O)<sub>2</sub>R16', N(R17')<sub>2</sub>, NR18'C(O)R19', NR20'SO<sub>2</sub>R21', SR22', S(O)R23', S(O)<sub>2</sub>R24', and S(O)<sub>2</sub>N(R25')<sub>2</sub>; and wherein aryl-C<sub>0</sub>-C<sub>4</sub>-alkyl, arylhetero(C<sub>1</sub>-C<sub>4</sub>)alkyl, heteroaryl-C<sub>0</sub>-C<sub>4</sub>-alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0</sub>-C<sub>2</sub>-alkyl are each
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optionally substituted with from one to three independently selected from R28; and wherein R10 and R11 optionally combine to form a 5 to 6 membered fused bicyclic ring with the phenyl to which they are bound:

- (l) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23',  
5 R24', and R25' are each independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl and aryl;
- (m) R30 is selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, aryl-C<sub>0-4</sub>-alkyl, arylhetero(C<sub>1-4</sub>)alkyl, heteroaryl-C<sub>0-4</sub>-alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0-2</sub>-alkyl, and wherein C<sub>1</sub>-C<sub>6</sub> alkyl, aryl-C<sub>0-4</sub>-alkyl, arylhetero(C<sub>1-4</sub>)alkyl, heteroaryl-C<sub>0-4</sub>-alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkylaryl-C<sub>0-2</sub>-alkyl are each optionally substituted  
10 with from one to three substituents each independently selected from R31;
- (n) R32 is selected from the group consisting of a bond, hydrogen, halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, and C<sub>1</sub>-C<sub>6</sub> alkyloxo; and
- (o) — is optionally a bond to form a double bond at the indicated position.

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AMENDED SHEET